REMARKS

Reconsideration and withdrawal of the objection to and rejection of the claims, in view of the amendments and remarks herein, is respectfully requested. Claim 7 is amended. Claims 1-7 are pending.

A copy of the information listed on the 1449 Form filed on January 9, 2006, and a copy of the Information Disclosure Statement and 1449 Form filed on January 9, 2006, are submitted herewith, so as to comply with the provisions of 37 C.F.R. § 1.97 and § 1.98 and M.P.E.P. § 609.

Claim 7 was objected to under 37 C.F.R. § 1.75(c) as being in improper form. The amendments to claim 7 obviate the objection thereto.

The specification has been amended to add sequence identifiers. The paragraph beginning on page 7, line 1, of the specification has also been amended. A substitute SEQUENCE LISTING is also filed herewith.

Support for the amendment to SEQ ID NO:21 in the SEQUENCE LISTING can be found at page 7, line 9.

Support for the amendment to SEQ ID NO:9 in the SEQUENCE LISTING and on page 7, line 29, can be found on page 7, lines 13-14, where it is stated that "[p]lasmid psiUb-lam and psiUc-lam were obtained by cloning in the BglII and XhoI sites of psiUx the following oligos...." Applicant respectfully submits that the appropriate 5′ end of a nucleic acid molecule which has been digested with XhoI is "TC...." Thus, the amendment to SEQ ID NO:9 in the SEQUENCE LISTING and to the sequence present on page 7, line 29, is supported by the application as originally filed.

Support for the amendment of SEQ ID NO:23 in the SEQUENCE LISTING can be found in Figure 2A, see for example, the lower strand of psiUc-lam/psiUd-lam/psiUc$_{mut}$-lam, where it is noted that the nucleic acid was digested with XhoI. As discussed above, the appropriate 5′ end of a nucleic acid molecule which has been digested with XhoI restriction endonuclease is "TC...." Thus, the amendment to SEQ ID NO:23 in the SEQUENCE LISTING is supported by the application as originally filed.

Applicant respectfully submits that SEQ ID NO:25 was presented in the SEQUENCE LISTING in the 3′ to 5′ direction. Applicant has herein corrected SEQ ID NO:25 in the

SEQUENCE LISTING to be in the 5′ to 3′ direction. Support for this amendment can be found in the lower part of Figure 2A.

The above-referenced substitute SEQUENCE LISTING is enclosed herewith to conform the above-referenced application to the requirements of 37 C.F.R. §§ 1.821-1.825. In accordance with 37 C.F.R. § 1.821(e), a copy of the above-submitted SEQUENCE LISTING in ASCII computer readable form is submitted herewith. It is respectfully submitted that the contents of the paper version of the SEQUENCE LISTING and the computer readable form are the same. It is further submitted that the paper copy of the SEQUENCE LISTING and the computer readable form of the SEQUENCE LISTING do not represent new matter.

Claims 1-6 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kreutzer et al. (U.S. published application No. 20040001811), Elbashir et al. (Methods, 26:199 (2002)), Hernandez (EMBO, 4:1827 (1985)) and Skuzeski et al. (J. Biol. Chem., 259: 8345 (1984)). This rejection is respectfully traversed.

Kreutzer et al. disclose a double stranded (ds) RNA with a RNA strand having a region that is less than 25 nucleotides in length and complementary to at least a portion of a RNA transcript of an anti-apoptotic gene such as Bcl-2. Kreutzer et al. also disclose that the individual strands of a dsRNA can be expressed from two separate vectors or from the same vector, or as an inverted repeat joined by a linker polynucleotide so as to form a stem and loop structure, and that the promoter can be a PolI promoter, PolII promoter, PolIII promoter or a prokaryotic promoter. However, the ssRNAs used to prepare dsRNAs for transfection in the Examples were prepared by conventional oligonucleotide chemical syntheses.

Elbashir et al. disclose the use of small interfering RNAs (siRNAs; 21 to 23 nucleotides in length), which are the products of RNase III digestion of dsRNAs formed with mRNA, to silence genes in mammalian cells. It is disclosed that the predominant siRNAs formed in cells are 21 and 22 nucleotide RNAs with symmetric 2 nucleotide 3′ overhangs (see Figure 4B which shows "TT" overhangs). Elbashir et al. disclose that 21 nucleotide RNAs useful to form siRNAs are prepared via conventional oligonucleotide chemical syntheses and annealed prior to transfection.

Hernandez discloses a vector to detect the processing of U1 nuclear RNA, which is transcribed by PolII and is involved in mRNA splicing. The vector includes an internally deleted

U1 gene expressed from the SV40 promoter/enhancer. The vector was introduced to cells and the resulting RNA analyzed. The results showed that the first U1 RNA precursor has a few extra nucleotides at the 3′ end which are shortened to form mature U1 RNA, and that a 13 nucleotide sequence 3′ of the coding region is required to direct the first step in the formation of the 3' end of U1 snRNA.

Skuzeski et al. disclose the identification of two regions at the promoter essential for transcription of human U1 RNA and that there is a *Bgl*II site immediately 5′ to the U1 coding region (Figure 5).

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to make a siRNA comprising 3' UU overhangs as taught by Elbashir et al. and include a termination sequence, as taught by Henderson [*sic*], into the expression vector, and to clone the U1 snRNA promoter into the expression vector using a *Bgl*II restriction site for the reasons taught by Skuzeski et al. The Examiner continues asserting that one of ordinary skill in the art would have looked to Elbashir et al. while making a siRNA as taught by Kreutzer et al. in order to design the optimal siRNA which includes 3' UU overhangs, that one of ordinary skill in the art would have wanted to use a termination sequence in an expression construct given that Nielsen et al. (note that Nielsen et al. is not cited in support of the rejection of the claims on page 4 of the Office Action) teach such sequences are preferred when constructing an expression vector to express inhibitor RNAs, and that one of ordinary skill in the art would have wanted to use the 3' end of a U1 snRNA promoter as a termination sequence given that Henderson [*sic*] teach specific conserved sequences of the 3' end of the U1 snRNA gene is required for formation of mature transcripts by a U1 snRNA promoter.

Nevertheless, none of the documents relate to the use of a U1 promoter to produce siRNA or miRNA from a vector. Rather, each of the documents relating to siRNA employs conventional oligonucleotide chemical syntheses to prepare individual ssRNAs and the U1 based vectors in Hernandez and Skuzeski et al. were employed to detect *cis*-acting elements in the U1 gene.

Moreover, none of the cited documents individually or in combination with each other disclose or suggest an expression vector which allows for the expression of a functional double-stranded molecule that can be recognized and correctly processed after transcription from a PolII

(U1-type) promoter by cellular machinery. In particular, transcripts expressed from the vectors of the invention have to be correctly processed by the enzyme Drosha in the nucleus and by Dicer in the cytoplasm, while synthetically prepared dsRNAs (Kreutzer et al. and Elabashir et al.) are not processed in the nucleus.

Further, even if a UU sequence is added, transcripts from a PolII promoter may not terminate, e.g., the promoter may still rely on a specific termination sequence.

The Examiner also asserts that the benefits of expression vectors comprising U1 snRNA promoters and the required 3' U1 snRNA gene termination sequences are well known in the art as well as the expression of therapeutic RNAs using U1 RNA PolII promoters. Pursuant to M.P.E.P. § 2144.03, Applicant respectfully requests a reference or an affidavit of personal knowledge by the Examiner to support these assertions in the next official communication.

Applicant's specification discloses that the U1-based vectors of the invention have few sequence requirements at the 5' and 3' termini of the transcripts; they accept U sequences in the transcribed region, unlike PolIII containing vectors; primary transcripts derived therefrom are efficiently exported to the cytoplasm and converted to the mature form; and specific sequences can be added at the 5' and 3' termini, that allow the selection of only one of the two siRNA strands to be incorporated into the interference complex. This eliminates the accumulation of the sense strand that could mediate undesired targeting. In addition, as shown in Figure 3B, a vector of the invention provides transcripts that have specificity and provide for significant interference.

Accordingly, withdrawal of the § 103 rejection is respectfully requested.